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Pharmacogenomics: sex differences and application in pediatrics

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Abstract

Pharmacogenomics is a promising field which increasingly influences medicine and biomedical research in many areas. The aim of this article is to review recent advancements in the understanding of genetic polymorphisms and their influence on interindividual variability in drug response. Also, the main variabilities in drug response according to sex differences will be discussed. The translation of pharmacogenomics into the clinical routine as well as the challenges of achieving the goal of personalized medicine are also discussed. The role of pharmacogenetic tests in pediatrics has not been well defined yet, but it is clear that those tests could help in resolving some issues regarding the administration of drugs to children. At the conclusion, the foremost ethical, social and regulatory issues regarding the translation of pharmacogenomics into clinical practice and future perspectives in the field will be discussed.

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Introduction

Inter-patient variations in drug responses are a notable obstacle in everyday clinical practice. While a particular drug can be efficient and safe to administer in the majority of treated patients, in some individuals it might be ineffective and/or cause adverse drug reactions (ADRs), which may also sometimes be life-threatening (1). Both genetic and environmental factors influence the drug response of an individual patient (2). Since inter-individual variabilities in drug response are often genetically determined, the field of pharmacogenetics evolved for the purpose of assessing the influence of specific genetic biomarkers on the efficacy and safety of drugs. Pharmacogenomics, which emerged from pharmacogenetics due to the appearance of genome-wide association studies (GWAS), analyses the entire genome to find multigenetic factors related to an individual's drug response,

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representing another step towards personalized medicine (2-4). Furthermore, pharmacogenomics represents a promising area for the aims of maximizing the benefits of pharmacotherapeutic regimens and minimizing the risks of developing ADRs, which are significant causes of morbidity and mortality in patients worldwide (5-7). Most genetic biomarkers that have been found to affect the drug response in pharmacogenetic and pharmacogenomic studies are variations in the DNA sequences of genes encoding both enzymes and transporters included in the absorption, distribution, metabolism and excretion of drugs (8).

Pharmacogenetic and pharmacogenomic trials are usually designed by three different methodologies: candidate gene studies, genome-wide association studies, as well as whole-exome and whole-genome sequencing (9). In candidate gene studies, a hypothesis-driven approach is used, where a single targeted gene, encoding a protein included in the metabolism of the drug, is investigated (9, 10). However, in GWAS, two groups of patients with a different drug response profile are compared, and potential associations with many known genetic variants are investigated (9). The third and most comprehensive methodology is whole-exome and whole-genome sequencing, where all human genetic material is analyzed for variants related to drug efficacy and safety. However, the analysis of data collected in such studies remains difficult (9).

Genetic polymorphisms of drug-metabolizing enzymes

So far, data obtained from previous pharmacogenomic studies has yielded extensive reports about the genetic influence on treatment outcomes and side effect appearance (11).

Polymorphisms in genes encoding drug-metabolizing enzymes (DMEs), or transporters in phases I and II of the drug metabolism, often influence the drug response and determine the risk for the development of ADRs (12).

Single nucleotide polymorphisms (SNPs), minor insertions or deletions, as well as the amplification and deletion of gene copies, are genetic polymorphisms of DMEs (12).

More than 90% of human genes contain at least one SNP. Consequently, so far over 14 million SNPs have been discovered in the human genome (13). Factors that cause variations in drug response are complex and involve fundamental aspects of human biology (1).

However, several variants of DMEs have been discovered since the completion of the Human Genome project (1). As a reward for this laborious work, genetic polymorphism studies show clinically significant applications (1).

Altogether 57 cytochrome (CYP) genes encode CYP enzymes, which are subdivided into families, mainly involved in the metabolism of exogenous substances (14). Since CYP450 takes part in the metabolism of 65-70% of clinically used drugs, those enzymes play an especially significant role in the field of pharmacogenomics. In fact, CYP450 enzymes are responsible for 75-80% of all reactions of the phase I metabolism (15,16).

For instance, 20-25% of all marketed drugs are metabolized by CYP2D6, which is why its polymorphisms are very frequently investigated in pharmacogenomic trials (17,18). For example, it is the rate-limiting enzyme in the catalyzing process of tamoxifen's conversion intoactive metabolites, 4-hydroxytamoxifen and endoxifen. Therefore, CYP2D6 has a significant impact on the individual's response to tamoxifen therapy; as well it does for many other drugs (19).

A further example of the numerous CYP450 enzymes under pharmacogenomic investigation is CYP2C19, which catalyzes reactions in the metabolism of clinically important drugs, such as tolbutamide, glipizide, phenytoin, warfarin and flurbiprofen. More than 20 polymorphisms of genes encoding this enzyme have been studied, whereas the two most common variant alleles, CYP2C19*2 and CYP2C19*3, are null alleles, exhibiting reduced enzymatic activities (1, 18).

In addition, GWAS data confirmed previous discoveries, indicating the importance of DME variants in drug response (for instance, clopidogrel and CYP2C19), thus offering evidence for different levels of correspondence (12).

Also, more than 50% of the drugs used in clinical practice are metabolized by CYP3A4 in the human liver. So far, more than 20 variants of CYP3A4 are known. The frequency of individual CYP3A4 variants varies greatly across different ethnic groups and many of those variants exhibit altered enzyme activities, which means that polymorphisms of the CYP3A4 gene could be responsible for the difference in drug response between ethnic groups (1, 18, 20).

Recent studies have also emphasized the critical role of CYP2C19 polymorphisms for the therapeutic effects of clopidogrel. Furthermore, the importance of CYP2D6 polymorphisms for tamoxifen treatment appears to be relevant (12).

Importantly, non-CYP450 DMEs also play important roles in the metabolism of various drugs. Therefore, polymorphisms of genes encoding those DMEs also influence the therapeutic effect and could lead to potential adverse reactions after drug intake (1).

Pharmacokinetics and pharmacodynamics: sex difference

Even though the mechanisms are still not well understood, it seems that sex also plays a crucial role in the pharmacological response (21)(22). Generally, it is known that pharmacokinetic differences between men and women are more extensive compared with variations in pharmacodynamics (21). Some drugs frequently prescribed for the treatment of cardiovascular diseases, such as verapamil and amlodipine, show sexual dimorphism in their pharmacokinetic profile (14). Bioavailability of amlodipine slightly differed among sexes, with women showing higher bioavailability. However, after the adjustment of the obtained data to body weight, no significant SGD in the bioavailability of amlodipine remained (23). Some recent findings suggest that sex differences appear also in the field of pharmacogenomics (21).

Studies about sex-based differences in the response to pharmacotherapy show that women experience ADRs in a more frequent manner, and that those side effects may also be more severe compared with the ADRs in men (thiazolidinedione-induced bone fractures, iatrogenic long QT syndrome and iatrogenic systemic lupus erythematosus, etc.) (23). For instance, inhibitors of angiotensin converting enzymes (ACEIs) and antagonists of angiotensin receptors 1 (ARBs) are important compounds of therapeutic regimens in the treatment of cardiovascular diseases (14). Investigations have reported that during treatment with ACEIs, cough and angioedema are more frequent in women than in men. Furthermore, it has been shown that the XPNPEP2 C-2399A genotype is associated with an increased frequency of ACEI-associated angioedema in black men, but not in white men and women (21, 22). Because of this circumstantial evidence for the unfavorable safety profile in women, further studies should be conducted to clarify sex-gender related differences (23). Importantly, sex differences in drug response could have various reasons, and they are not all caused by the varieties of the DNA sequence of pharmacogenetically-relevant genes (24).

Due to the fact that not many genes that are known to be relevant for pharmagenomic studies are located on sex chromosomes, sex-gender differences in drug response are possibly caused by differences in autosomes, transcriptional gene regulation due to sex-specific epigenetic modifications, posttranscriptional modifications or by the effect of sex hormones (24, 25). Although animal studies suggest that sex-specific expression of CYP isoforms is a common case in rodents, this mechanism is subtler in humans (20). However, sex dimorphic metabolism does occur also in humans, for instance in the case of CYP3A4, as a very important isoform of CYP, which is expressed more extensively in females than in males (20).

Furthermore, evidence for sex-gender dependent gene expression exists, and this sexually dimorphic expression is seen in liver, muscle, fat and brain tissue (26, 27). Also, frequencies of specific allelic polymorphisms are unequally distributed among men and women, which also contributes to differences in the drug response and safety profile (24). Furthermore, psychological, physiological and lifestyle factors influence sex-gender differences, in particular in the case of therapy outcomes for drugs targeting the central nervous system (28,29). It is still unknown whether pathological conditions influence pharmacokinetic and pharmacodynamic parameters in a sex-gender dependent way (28, 29).

Until now, sex differences have been undervalued, and the study design in clinical trials during the drug approval process did not have a proper sex-based approach, all of which has led to a deficient understanding of drug response and side effect disposition among women, a deficiency that is a missing link in the path towards personalized medicine (21, 25). It is of great importance to carry out further studies with a more sex-based approach, so that it would become possible in the future to better adjust pharmacotherapeutic regimens and individual drug doses according to the sex of the patient (21).

Translating pharmacogenomic knowledge into clinical practice

The main long-term goal of pharmacogenomics is to translate observations regarding the genetic basis of drug responses into a more effective and less toxic treatment for individual patients in the everyday clinical practice (30). Until now, due to detailed pharmacogenomic studies for some drugs, the clinical application of this branch of personalized medicine has already become possible (9). Examples of successful clinical application of pharmacogenomics are listed in Table 1 (9).

Pharmacogenetic testing, in order to determine the suitability of a drug for the individual patient, is gradually moving from specialty medications, for instance drugs prescribed for patients with cancer, to more broadly prescribed medications, as are statins, codeine or warfarin (31).

Heretofore, the drug labels of 137 medications include pharmacogenetic-related information (32). It has been estimated that 16 percent of medications prescribed in primary care are pharmacogenetically impacted (33). The delivery modes of pharmacogenomic testing are yet unclear; therefore, the main goal is to write clinical practice guidelines with decision-making algorithms informed by controlled-clinical pharmacogenomics trials (34-37). These guidelines may increase precision, accuracy and the relevance of recommendations and subsequent applicability (38). Although pharmacogenomics offers significant potential to improve the clinical outcome of individual patients, the translation of pharmacogenomic knowledge and principles into clinical practice has been slow in most settings (30). One of the reasons could be the fact that in many cases, the variability of drug response involves many different factors other than pharmacogenomics (1). In fact, the understanding of the pathophysiological processes of the disease, the identification of important genes, as well as the recognition of the roles the genetic polymorphisms of receptors, transporters or DMEs play in the pharmacological outcomes, are all required for the complex process of achieving individualized medicine (1). For the reason that many factors that are not reflected in genomic information influence drug toxicity and efficacy, it is questionable whether personalized drug treatment will ever become attainable by pharmacogenetic testing alone (1). In addition to scientific difficulties, economic, ethical, social and regulatory issues are also very challenging (1).

Pharmacogenomic applications in pediatrics

During the past decade, much effort has been devoted to improve the safety and efficacy of medical products used for the treatment of the pediatric age spectrum, from premature newborns to adolescents, with a special accent

Table 1. *Examples of clinically relevant pharmacogenomic testing.*

Drug	Genetic variants	Influence	Notes
Warfarin *anticoagulant drug*	CYP2C9 gene and VKORC1 (78)	Genetic polymorphisms impact dose requirements of warfarin therapy (9, 79)	Only 59% of US patients have INR 2-3 (because of the narrow therapeutic range of warfarin many patients still receive an incorrect dose) (80)
Simvastatin lipid-altering agent used to treat hypercholesterolemia	SL-CO1B1*5 (81)	Increased risk of statin-induced myopathy patients suffering from cardiovascular disease (82)	Simvastatin is a widely used drug: SL-CO1B1 testing could reduce the incidence of statin-induced myopathies or rhabdomyolysis(83)
Codeine opioid analgesic drug	CYP2D6 (84)	Genetic polymorphisms affects metabolizing phenotype of patients (84)	Metabolizing phenotypes: ultra rapid (high risk for ADRs) and extensive metabolizers to intermediate and poor metabolizers (inadequate analgesia) (84)
Geftinib EGFR tyrosine kinase inhibitor (TKI)	EGFR (85)	EGFR mutation is a biomarker of geftinib efficacy (86, 87)	BRCA1 as well as compounds of the NF-κB pathway also affect the response of EGFR mutated patients to geftinib (88)
Irinotecan chemotherapeutic drug used for colorectal cancer	UGT1A1*28 (89)	UGT1A1*28 polymorphism leads to lower protein expression and irinotecan-induced toxicity (hematological and digestive ADRs) (89, 90)	Irinotecan is a prodrug of SN-38 that is conjugated via UGT1A1 (90)

on the progress in dosing strategies. Since the medicine registration protocols of the European Union, before the legislation called Paediatric Regulation in 2006, did not obligate pharmaceutical companies to assure in advance a Pediatric Investigation Plan (PIP), as reported by the European Commission, between 50% and 90% of the drugs used in pediatric medical care were administered off-label, without being adequately tested nor authorized with a tolerable risk benefit profile in children (39-41). There are two main issues regarding the administration of drugs to children under these circumstances. On the one hand, doses for children are usually obtained empirically in the absence of evidence by adapting adult doses to body weight in a trial-and-error pattern (42). Since absorption, disposition, metabolism and drug elimination are subject to developmental processes due to the ontogeny of DMEs, pharmacokinetic responses are not equivalent to those during adulthood (40, 43-45). Thus, dosing protocols for children should be independently obtained in pediatric studies.

On the other hand, along with changes in enzymatic activity due to the changes of gene expression during the development process, which is specific for the pediatric population, the influence of SNPs of genes for some receptors, enzymes and transporters involved in drug response and metabolism, also plays a fundamental role in the accurate prediction of treatment response in children (44, 46).

Consequently, additional pharmacogenomic trials should be performed in children if relevant biomarkers are available, since only about 70% of pharmacogenomic data obtained from studies on adult populations can be applied to children (45, 47-50). The role of pharmacogenomic tests in pediatrics has not been well defined yet and there is a lack of genotype-guided dosing strategies for children (51-53). Compared to adults, children have an increased level of complexness due to physiological maturation processes, as well as the ontogeny of gene expression, which contributes to the influence of specific genetic variants investigated in pharmacogenomic trials (54). As a result, the approach to results from pharmacogenomic trials on children should differ substantially from those yielded in studies on adult patients (54). Even though the DNA sequence persists throughout life, the pattern of gene expression is dynamic, and changes in protein synthesis occur. Indeed, some of the most important enzymes involved in drug metabolism, like CYP450 and UDP glucuronyl transferase, display gene expression depending on developmental changes (55). For instance, CYP3A7 gene expression is already observable in the fetal liver during the first trimester of pregnancy, but the level of CYP3A7 enzyme production decreases after the immediate postnatal period. As the CYP3A7 level of gene expression decreases, CYP3A4 and CYP3A5 expression boost after the end of the first postnatal week, until they reach 30% of the adult enzyme activity levels by the end of neonatal period (55, 56). Although the overall level of CYP3A protein expression remains constant, differences in specificities to substrates, as well as metabolic and catalytic capacities exist, depending on whether the prevailingly expressed genetic variant is CYP3A7 or CYP3A4 (55). Thus, drug metabolism via the CYP3A subfamily varies due to developmentally regulated gene expression and, depending on the moment of drug administration during the neonatal period, genetic variants in different members of the CYP3A subfamily are important. For instance, this might play an important role in altering the pharmacokinetics of tacrolimus, a calcineurin inhibitor and immunosuppressant drug used in children and adults after solid organ transplantation (57, 58). Since tacrolimus has a very narrow therapeutic index, it is still challenging to adjust the dosing regimen in children so that further pharmacogenomic trials and its implementation into clinical practice could potentially be crucial in this process (43, 59). Due to the breakthrough of pharmacogenomics in the field of personalized medicine, a number of pharmacogenomic studies are being conducted, mainly with adults as subjects in those trials. However, even though pharmacogenomic research on children lags behind, results published so far in this field accentuate the difference between children and adults in the framework of pharmacogenomics (54, 60). Therefore, it would be vague to directly extrapolate data from adult pharmacogenetic trials without putting them into the variable pharmacokinetic context of a developing child (54, 61). Indeed, there are some well-known clinical utilizations of pharmacogenetic tests in adult medical care, but there is still a lack of knowledge to translate those results to the pediatric patient spectrum (60). The most significant achievements in this study field have been made in pediatric hematology and oncology, but some trials were also conducted in the areas of rheumatology, endocrinology, neurology, gastroenterology, pulmology and organ transplantation in children (46, 54). For example, one of the most frequent chronic diseases in children is juvenile idiopathic arthritis (JIA), which can lead to persistent disabilities in adulthood (65). Methotrexate (MTX) is a disease-modifying antirheumatic drug (DMARD) important in the treatment of JIA that unfortunately exhibits heterogeneity in the clinical response (64). Pharmacogenomic studies suggest that polymorphisms in many genes encoding products included in the disposition and biochemical pathways of MTX, for instance, CACNA1I, ZMIZ1, TGIF1 or CFTR, can affect the clinical outcome and therefore have the potential to make pharmacogenetic testing of individual patients an integral diagnostic component before the application of MTX therapy (62-64).

Moreover, since pharmacogenomics seems to be one of the emerging tools used to improve drug safety by the avoidance of giving specific drugs to susceptible individuals who are likely to develop adverse drug reactions (ADRs), it is important to consider that some ADRs are specific to, or more frequent in, children. In fact, it is in some cases unreasonable to assume the genetic influence on the occurrence of some ADRs through adult pharmacogenomics study results, if these ADRs are unique to the child population (54).

Ethical issues concerning pharmacogenomics

Apart from the recognized benefits of pharmacogenomics in the future perspective of patient medical care, considerable ethical and legal questions, which could eventually overwhelm the unprepared legal framework, are arising (66). First of all, pharmacogenetic testing should not be administered without a signed informed consent, containing appropriate information about the benefits and risks of the procedure (67). Due to a child's inability to fully understand, or understand at all, the purpose and possible aftereffects of pharmacogenetic testing, parents or legal guardians must sign the consents. The ethical issue addressed here is that a person who signs the informed consent is not the person who receives the genetic testing, which could have unforeseeable consequences (68). As well as in other genetic tests, the DNA sample primarily used for one purpose, in this case, obtaining data about the individual efficiency and safety of a patient's treatment could unintentionally yield additional secondary information. Secondary information could be information about a predisposition to several diseases, a prognosis of current illness, or pharmacogenetic information about drugs used for other conditions, which could lead to both a patient's psychological and economical discomfort. For example, if the patient with a disease would be classified as a nonresponder to drugs currently used for the treatment of his condition, this could have an impact on the patient's insurance payments or even lead to discrimination in their search for employment because of the additional health care costs for employers (68, 69). Consequently, this example also raises the question of confidentiality and who should have access to data obtained by these tests. Also, if the patient, for instance, undergoes testing for the apolipoprotein E genotype, which is the most frequently investigated pharmacogenetic biomarker for statins, he might also receive unwanted information about his risk of developing Alzheimer's disease in his elderly years (70, 71). Also, due to the possible high costs of pharmacogenetic testing, it is likely that the economic status, whether of an individual patient or of a whole country, will influence and limit the accessibility of the method. Correspondingly, this could enhance the unethical socioeconomic divisions and inequalities in the health care system (72, 73).The pathway towards personalized medicine entails that the drug development by pharmaceutical companies should be genetically guided. Due to the further costs involved in such drug design, pharmaceutical companies might first want to evaluate the frequencies of alleles of interest. In the case of limited profits from the restricted drug market due to rare alleles and genotypes of nonresponders to available drugs, pharmaceutical companies might not be intrinsically stimulated to develop new drugs for those individuals. Just like in the case of orphan drugs for rare diseases, drug development for rare, orphan genotypes should be economically stimulated (72, 74, 75). In addition to the problem of orphan genotypes, it could be the case that developing drugs even for very frequent genotypes would not be of interest to major companies if the genotypes were geographically located in socioeconomically poorer areas (72).

Despite the ethical and legal questions, it seems that pharmacogenetic testing is one of the most promising steps towards personalized medicine. However, effort should be put into establishing legal parameters that can cope with the emerging needs of the evolving field of pharmacogenomics.

Future perspectives

Further trials with even more participants are likely to yield results in the near future that could extend the number of clinical implementations and make another step towards personalized medicine (76). Since the field of pediatric pharmacogenetics still falls behind the research on adults, advances in the research field are still expected so that the complex compound of genetic influence and ontogenic dynamics in children could be understood. A better and more profound explanation of those processes would certainly facilitate the clinical implementation of the future collected knowledge in the field of children's pharmacogenomics (51).

Furthermore, it is of great importance to educate clinicians about data interpretation of pharmacogenetic test results so that they can gain the required knowledge to accurately stratify patients into high-risk or low-risk groups regarding drug toxicity and consequently improve the therapeutic outcome without putting susceptible patients at risk of predictable life threatening ADRs. Therefore, new user-friendly and up-to-date guidelines should be provided to clinicians in order to help the future implementation of pharmacogenomic study results into the clinical daily routine (43, 46, 77).

It is likely that the further use of next-generation sequencing will lead to new advances in pharmacogenetics (43). Also, although still expensive, high-throughput screening methods could become more affordable in the future and help progress in the scientific field (77). Hence, these and further technological improvements could upgrade the current knowledge in pharmacogenomics to an advanced level, which could lead to more clinical aims, consequently increasing the safety of drugs used for the treatment of many diseases. However, since there are also emerging ethical concerns, an adequate legal framework should be established.

Conclusion

Pharmacogenomics is a rapidly emerging and promising scientific field in which an increasing amount of studies are being conducted. Although there are still challenges, it is promising that they could vanish with the improvement of study designs and the formation of international cooperation that would validate pharmacogenomic study results and promote the clinical use of pharmacogenetic tests (76). Sex-related differences have been reported in pharmacogenomics trials. Since more severe and more frequent drug adverse reactions have been found in women, whose pharmacological status is less studied, emphasis should be put on pharmacogenomic investigation in women (34). There are still no satisfactory data present regarding pediatric pharmacogenomic studies (54). However, legislations, both in the EU and USA, accentuate the need for clinical trials on pediatric patients so that an admissible level of safety in drug administration could be reached (40). The process of achieving individualized medicine for many diseases is complex, especially considering that many nongenetic factors influence drug toxicity and drug efficacy. In addition to scientific difficulties, economic, ethical, social and regulatory issues are also very challenging (1).

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